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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/086,542	02/28/2002	Geoffrey M. Wahl	SALK1790-6 (088802-3457)	2411

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EXAMINER	
BERTOGLIO, VALARIE E	

ART UNIT	PAPER NUMBER
1632	10

DATE MAILED: 06/17/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/086,542	WAHL ET AL.	
	Examiner	Art Unit	
	Valarie Bertoglio	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 May 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *02/28/2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Response to Amendments

Applicants' arguments file 05/06/2003, paper number 9, have been fully considered and are found partially persuasive. Claims 1-19 are pending and under consideration in the instant action. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior office action.

Claim Rejections - 35 USC § 112

Applicants' arguments pertaining to the rejection of claims 1-19 under 35 U.S.C 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, see paper #9 pages 5-6, have been fully considered and are persuasive. The written description rejection of claims 1-19 has been withdrawn.

The rejection of claims 1-19 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention is maintained.

The purpose of the claimed transgenic animals are to: 1) allow for site-specific insertion of an FRT- transgene construct by homologous recombination with an FRT site within the genome of an animal (claims 1, 3-8, 11, 15, 16; refer to specification page 4, para. 0011), 2) allow for directed activation of a gene by removal of an FRT-flanked disruption using FLP-induced homologous recombination between FRT sites located within said gene (claims 2,9,10,12,17,18; refer to specification page 4, para. 0010), and 3) to insert a gene disruption construct by FLP-induced homologous recombination with a nondisruptive FRT located within a gene of interest (claims 2,9,10,13,14,17,19; (refer to specification page 20, para. 0063). The teachings in the specification demonstrate the use of the FLP/FRT recombination system in mammalian cells, in vitro for purpose 2 (pages 13-19, Examples 1 and 2) and purpose 3 (pages 20-21, Example 3).

The state of the art at the time of filing held that it was unpredictable how to obtain the phenotype of interest, including physiological, anatomical or molecular phenotype, in transgenics. The expression level of a transgene is dependent upon a large number of variables including position of integration, promoter used, gene encoded by the transgene, noncoding sequences incorporated into a transgene, and the species of animal used. Examples in support of the unpredictability of transgeic techniques can be found in the previous office action.

Applicants' arguments pertaining to the rejection of claims 1-19 under 35 U.S.C 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, see paper #9 pages 6-8, have been fully considered and are not persuasive.

1) The specification does not enable using any of the 3 strategies described in the specification to make FLP-recombinant transgenics (claims 1-19) because it does not provide the guidance necessary for one of skill in the art to prepare transgenic animals and obtain levels of FLP-recombinase sufficient to induce FLP-mediated recombination in vivo. The specification contemplates introducing FLP recombinase to an animal by administering the enzyme as a protein, by breeding with a transgenic expressing the enzyme, or by transfection with DNA encoding the enzyme (page 12, paragraph 0038).

The specification does not teach the levels of FLP recombinase activity needed to reach the nucleus to allow for recombination at FRT sites of an animal, which differs for various sites of integration and are random in this invention because the specification fails to describe any specific integration sites. The specification does not address how to deliver the recombinase enzyme to cells of an animal without disrupting recombinase activity by denaturation or degradation. One could use transgenesis to deliver a gene encoding FLP to an animal to avoid the possibility of degradation or denaturation. However, when using transgenesis as a means of delivering FLP recombinase in vivo, as discussed above, the state of the art at the time of filing was that, due to variables such as the promoter, position effect, species and genetic

background, the phenotype of a transgenic animal is unpredictable. The state of the art also held that the level of recombination induced by FLP recombinase at FRT sites, in vivo, was dependent upon the level of FLP recombinase expressed (Golic, 1989, Cell, Vol. 59, pp. 499-509, specifically page 507, first full para; Dymecki, 1996, PNAS, Vol. 93, pp. 6191-6196, specifically page 6195, last sentence-page 6196 lines 1-3). Importantly, the specification discloses substantial differences in detectable levels of recombination dependent upon the cell line used (page 17, para. 0055). In vivo, the FLP recombinase gene would be stably integrated in the genome of the animal, as opposed to being introduced as a plasmid, and the amount of FLP recombinase required to cause recombination in vivo and how to achieve this level of expression in vivo is unknown. The specification teaches in vitro transient transfection of cells with plasmid comprising a CMV promoter driven FLP recombinase gene (for example see page 16, para. 0054). The specification does not provide adequate guidance to apply this technique in vivo. Due to the unpredictability of phenotype, including molecular phenotypes, in transgenics, the unpredictability of the amount of FLP required to obtain recombination at an unknown FRT locus in vivo, and the dependence of recombination activity on the level of FLP recombinase obtained, it would require one of skill in the art undue experimentation to determine how to prepare transgenic animals such that sufficient levels of FLP recombinase are expressed to induce detectable of FLP-mediated recombination. A further variable involves the site of integration of the FLP transgene as position effects can affect the expression of the recombinase gene. One of skill in the art would need to know the 1)intended site of FRT integration, 2) the structure of the FLP transgene, 3) the promoter of the FLP transgene and 4) the site of integration of the FLP transgene, to make and use the claimed invention.

2) The specification does not enable inserting a transgene into a specific locus within the genome. Applicant argues that the site of integration of an FRT can be determined using techniques well-known in the art and that a FLP transgene or FRT transgene can be homologously recombined with a known site. Applicants argue that in the claimed invention, the recombination event is controlled by the action of FLP

recombinase on the FLP recombination target site and that the position of the FRT can be controlled by methods known in the art. However, the specification provides no guidance as to what the preferred sites of FLP integration may be or how to determine them. Random insertion of the FRT site would not work because of position effects (Wall, 1996, Theriogenology, Vol. 45, pages 57-68; Dymecki, 1996, PNAS, Vol. 93, pages 6196-6196) and would not provide utility over standard transgenic techniques without additional, undue experimentation. Therefore, it would require one skilled in the art, undue experimentation to determine how and where to insert an FRT into the genome to enable one of skill in the art to use the invention.

3) The specification further fails to provide a means for introducing, in vivo, a transgene designed for insertion into an FRT site as the specification described for cells in culture (for example see page 20), and as encompassed by claims 13-19 (purposes 1 and 3). It is not clear how one would provide a transgene to an animal and have that transgene maintained in cells until a chosen time of FLP recombinase expression. It is possible to readily introduce DNA into cells, in vitro, concomitant with FLP recombinase expression, allowing for temporal control of transgene insertion and subsequent expression or disruption of expression, as described in the specification. Doing so in ES cells would provide a means of generating a transgenic animal, however, because the FRT site is randomly inserted in the genome (see previous paragraph) of the ES cell, the resulting recombinant is no different than that of a standard technique of generating transgenics and, importantly, would not allow for the asserted use of temporally controlling transgene insertion. Thus, recombining a transgene into an FRT site in an ES cell, would not satisfy any of the advantages of this system as taught by the specification such as spatial or temporal control of transgene insertion, activation or inactivation (page 2, paragraph 005) or insertion of transgene into a desired location (page 2, paragraph 004) and the specification and fails to provide any guidance as to any other means of delivering a transgene to cells of an FRT-transgenic mammal such that the delivered transgene is inserted at the FRT site.

4) The specification does not enable the use of a transgenic mammal comprising an FRT site to provide a functional gene by FLP-mediated recombination (purposes 1 and 2). The specification fails to disclose how to insert the described β-galactosidase-FRT-disrupted transgene into the genome such that, after excision of the disruption, the active, recombined transgene is expressed to detectable levels. Dymecki (1996) used the strategy described in Figure 1B of the specification (purpose 2) in mice and it did not result in the expected expression of the recombined β-galactosidase transgene. Flp-mediated excision of an inactivating region did occur; however, β-galactosidase activity was not functionally and detectably expressed due to the position effects surrounding the FRT site (Dymecki, page 6196, column 1, lines 43-46), which is random in both the instant invention and in Dymecki. In fact, to avoid this limitation, Awatramani (2001, Nature Genetics, Vol. 29, pages 257-259) targeted an FRT-disrupted PLAP gene to the ROSA26 locus, known to be broadly expressed both spatially and temporally throughout development (Soriano, 1999, Nature Genetics, Vol. 21, pages 70-71), to ensure expression of the activated, recombinant PLAP gene upon FLP-mediated removal of inactivating sequences. It would require one of skill in the art at the time the invention was made, undue experimentation to determine how to insert a transgene such that levels of expression are such to obtain a desired activity or phenotype upon FLP-mediated transgene activation.

5) The specification does not provide adequate guidance for one of skill in the art to generate and use transgenic rats, monkeys or hamsters (claims 6-8 and 15-19). As discussed above, the phenotype of a transgenic is unpredictable and closely related species carrying the same transgene construct can exhibit widely varying phenotypes. Furthermore, transgenic mammals other than mice can only be chimeric because it is not known in the art how to generate transgenic mammals, other than mice, that transmit a transgene through the germline to the non-chimeric, F_1 generation. The phenotype of chimeric, transgenic animals is made further unpredictable by the fact that it cannot be predetermined which cells of the animal will carry the transgene. Furthermore, the specification contemplates introducing FLP

recombinase to said FRT-transgenic mammals by mating animals containing each of the two transgenes. Because transgenic mammals other than mice would not pass the transgene through their germline, the progeny would not contain either transgene. Without guidance as to how to generate the claimed rats, monkeys, or hamsters, it would have required undue experimentation for one of skill in the art to make and use a transgenic rat, monkey, or hamster carrying an FRT for the purposes outlined in the specification (see above) and claim 13.

Claim Rejections - 35 USC § 103

Applicants' arguments, see paper #9, pages 8-9, filed 05/06/2003, with respect to claims 1,3-5,15 and 16 have been fully considered and are persuasive. The rejection of claims 1,3-5,15 and 16 has been withdrawn.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Valarie Bertoglio whose telephone number is 703-305-5469. The examiner can normally be reached on Mon-Weds 6:00-2:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds can be reached on 703-305-4051. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1234.

Valarie Bertoglio
Examiner
Art Unit 1632

DEBORAH J. REYNOLDS
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